FRACTIONATION OF MAGNETIC MICROSPHERES FOR MAGNETIC DRUG TARGETING USING DEAN FLOW COMBINED WITH A MAGNETIC OCTUPOLE ON A CHIP

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ABSTRACT

We present a microfluidic-chip-based concept for continuous fractionation of magnetic microspheres (MMS) having a broad size distribution. Fractionation is achieved through a combination of shear-induced inertial lift forces that act on particles flowing through a curvilinear channel (i.e., Dean Flow) and magnetostatic forces produced by an octupolar arrangement of magnets mounted below the chip. The chip was designed, built, and tested using different MMS mixtures. The novel device enables the complete recovery of MMS from highly diluted suspensions, the separation of MMS mixtures, and size-dependent fractionation of MMS.

KEYWORDS: Dean force, fractionation, lab-on-a-chip, lift force, magnetic microspheres, microfluidic, separation

INTRODUCTION

Magnetic microspheres typically exhibit broad size distributions. For clinical magnetic drug targeting, it is preferable that these particles have uniform properties so that each one responds in the same way to externally-applied guiding magnetic field gradients and so that drug release kinetics are as homogeneous as possible. Additionally, MMS must be smaller than red blood cells but still large enough to react to applied magnetic field gradients. Since the preparation of monodisperse MMS can be challenging, there is considerable incentive to develop efficient size-dependent sorting (fractionation) techniques that can be used to produce narrow and well-defined particle distributions.

The goal of this investigation is the development and testing of a microfluidic chip for the continuous size-dependent fractionation of MMS based on both shear-induced inertial lift and magnetic forces.

THEORY

The primary fractionation mechanism in our device involves the influence of Dean-Flow [1] on suspended particles traveling through a curved channel. Depending on the flow velocity, the channel geometry, and the associated Reynolds number, a secondary flow pattern (Dean vortices) directed perpendicular to the channel axis (Fig. 1) is generated. Small particles entrained in this flow will circulate; however, particles larger than a certain size will tend to cluster near the inner wall. Size-dependent fractionation [2,3] can then be accomplished simply by splitting the flow into an inner and an outer stream. An additional level of control over the fractionation process can be obtained by imposing another force that acts toward the outer wall of the channel. In our experiment this is accomplished using a radially-directed magnetic field gradient.

EXPERIMENTAL

A long curvilinear channel was realized by a spiral structure (Fig. 2a) which was made using polydimethylsiloxane (PDMS) molding. The chip consists of an inlet (in) in the middle of the spiral, the spiral channel itself, and a 1:1 flow splitter.
on the outside of the spiral. The splitter separates the flow into inner and outer streams that can be collected at the inner (io) and outer (oo) outlets. The spiral channel has 5 windings, is 100 µm wide, 60 µm high, and has a total diameter of about 6 mm. Magnetostatic forces are generated by a magnetic octupole (Fig. 2b) built from 8 axially magnetized cuboids \((3 \times 3 \times 10 \text{ mm}^3)\). The octupole is mounted below the chip and positioned so its field-free axis passes through the inlet port (Fig. 3).

![Figure 2: Schematic of the (a) microfluidic MMS fractionation system with inlet (in), outer outlet (oo), and inner outlet (io) and (b) the octupole magnet that produces a strong radially-directed field gradient.](image)

Sterile filtered deionized water served as carrier for the MMS, which were circulated through the chip by a syringe pump. The suitability of the chip to separate distinct MMS size populations was confirmed through several experiments. The forces acting on the MMS were adjusted by changing the flow rate and the distance between the magnetic octupole and the chip. Different MMS dispersions were investigated:

A: Initial testing was performed using 6-µm-diameter MMS with a narrow size distribution. The total amount of MMS collected at the inner and outer outlets as a function of flow rate was determined by means of a hemacytometer (Hauser Scientific, Horsham, PA, USA).

B: A mixture of 2-µm and 12-µm-diameter particles (each with narrow size distributions) was then fractionated. The particles collected from the two outlets were characterized by static light scattering (Mastersizer 2000, Malvern Instruments, Malvern, UK) to determine the MMS separation efficiency as a function of flow rate.

C: MMS with a mean diameter of 3.5 µm but with a broad size distribution were then processed through the fractionation chip. The mean particle size and the polydispersity index (PDI) as a measure for the size distribution of the collected fractions were characterized by static light scattering and again studied as a function of flow rate.

![Figure 3: Photograph of the microfluidic chip (1) showing the spiral structure (2), inlet (3), and two outlets (4). The octupole magnet (5) is visible beneath the chip.](image)

RESULTS AND DISCUSSION

It was possible to drive all of the nearly monodisperse (6 µm diameter) particles to either the inner stream (via the Dean effect) or the outer stream (via imposed magnetostatic forces); see Fig. 4. In a different test, a mixture of particles with diameters of 2 µm and 12 µm was clearly separated by adjusting the flow rate. The 2 µm particles appeared in the outer stream (oo) and the 12 µm particles appeared in the inner stream (io), with 88% and 100% efficiencies, respectively.

A typical MMS batch with a broad size distribution and a mean diameter of 3.5 µm (PDI = 0.65) was also fractionated into samples with mean diameters of 2.8 (PDI = 0.48) and 4.3 µm (PDI = 0.54) (Fig. 5) by varying the flow rate but keeping the distance octupole to chip constant. The size distribution during this fractionation changed only slightly as shown by the polydispersity index (PDI) for the fractions which is only marginally smaller then for the original sample.
Figure 4: Fraction of particles collected at the inner and outer outlets as a function of flow rate with constant imposed magnetic field gradients (original sample: monosized MMS, 6 µm).

Figure 5: Mean MMS diameter at the outlet ports as a function of flow rate with constant imposed magnetic field gradients (original sample: polydisperse MMS, mean diameter: 3.5 µm).

CONCLUSION
The device investigated here is suitable for concentrating particles with desired size fractions and for excluding particles with sizes above or below a threshold. This separation is achieved via a continuous flow process instead of batch processing. For a given distance between the chip and the magnetic octupole, particle sizes can be chosen simply by adjusting the flow velocity of the carrier fluid.

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